

REMARKS

Claims 1-25 are pending in the application. Claims 11-25 are withdrawn from consideration as being drawn to a non-elected invention. Claim 3 has been canceled without prejudice or disclaimer. Claims 1 and 2 have been amended to better clarify what Applicants believe to be the invention. Support for the amendment to claims 1 and 2 can be found throughout the specification, but particularly in claim 3. New claims 26 through 28 have been added for consideration. Support for these new claims can be found throughout the specification and also in claims 1, 2 and 3 as previously presented. No new matter has been entered by way of this amendment. Accordingly, claims 1-10 and 26 through 28 are currently under consideration. Reconsideration of this application is respectfully requested.

Applicants' representatives would like to express their sincere appreciation for the courteous and constructive telephonic interview held with Examiners Susan Beth McCormick Ewoldt and Susan Coe on October 24, 2005 as related to the claims under consideration. As noted in that telephone conversation, Examiner Coe has kindly agreed to reconsider the Declaration under 37 CFR §1.132 executed by Dr. Ismail Elchagea, which was filed on June 29, 2005, attesting to the unexpected findings observed by Applicants in late stage hepatitis patients using a concentration of not less than 20% weight per volume of the plant compositions under consideration in the present application, which have been shown by Applicants to be effective at improving liver function and reversing the liver damage observed in these patients.

Rejection under 35 U.S.C. §102

- A. The Examiner has maintained the rejection of claims 1, 2, 4-6, and 8-10 under 35 U.S.C. §102, first paragraph for the reasons set forth in the previous Office Action. In particular, the Examiner alleges that Medenica (U.S. 5,653,981) teaches using an extract of *Nigella sativa* for increasing immune system function. The Examiner further alleges that Medenica also teaches how to administer the extract of *Nigella sativa* such as intramuscular, subcutaneous, intravenous, tablet, capsule, or suppositories or the like.

Applicants' Invention as Currently Claimed

The present invention, as currently claimed, is directed to a pharmaceutical composition, comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa* and *Ranunculus arvensis*, or extracts thereof, and a pharmaceutically acceptable carrier. In another embodiment, the present invention is drawn to a composition comprising a therapeutically effective amount of *Nigella sativa* and *Anemone hepatica*, or extracts thereof. More particularly, the claims have been amended to recite that the composition comprising at least one of the plants is present in a concentration of not less than 20% weight per volume. Support for the amendment can be found in original claim 3, which has now been canceled without prejudice or disclaimer. The composition may be delivered as a tablet or capsule, or in the form of a liquid or suspension. It may be delivered intramuscularly, subcutaneously, intravenously, intranasally, topically, transdermally, or in the form of a suppository. It may be used to treat hepatitis and to increase the number of immune cells and platelets in patients.

Moreover, one new independent claim and two new dependent claims have been added for consideration that recite the language from previously presented claims 1 and 2. More particularly, these new claims recite that the compositions as currently claimed may be used for treating advanced stage hepatitis patients, characterized as having fibrosis and cirrhosis of the liver as well as for increasing immune cells and platelets in patients.

The Medenica Reference

The Examiner alleges that Medenica teaches using an extract of *Nigella sativa* for increasing immune system function. The Examiner further alleges that Medenica teaches that the extract of *Nigella sativa* may be administered intramuscularly, subcutaneously, intravenously, by tablet, by capsule, or suppositories.

Claim Amendments and Arguments in Support of Patentability over Medenica

Applicants respectfully traverse the Examiner's rejection and assert that in order for a rejection under 35 U.S.C. §102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Medenica does not

teach the compositions of the present invention as currently claimed and that there are distinct differences between the teachings of Medenica and the present application.

For example, Applicants assert that Medenica teaches a pharmaceutical dosage form of *Nigella sativa* for inhibiting cancer cell growth. Applicants further assert that Medenica **neither teaches nor suggests a pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa and Ranunculus arvensis**, or extracts thereof, and a pharmaceutically acceptable carrier, **wherein the at least one of the botanical plants is present in a concentration of not less than 20% weight per volume**. In addition, Medenica does not teach or suggest a composition comprising a therapeutically effective amount of **Anemone hepatica and Nigella sativa, or extracts thereof, wherein the Nigella sativa is present in a concentration of not less than 20% weight per volume**. Furthermore, Medenica does not teach or suggest that the currently claimed plant compositions can be used for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, wherein the patients are in stage 4-6 of the disease process.

Applicants further assert that Medenica utilizes methods of isolating the extracts and concentrations of the extracts that are very different than those of Applicants. Such differences would not result in compositions that would be effective in treating the advanced stage hepatitis patients as described in the present application for the reasons noted herein. More particularly, the concentration taught by Medenica is 2.2%, not 20% weight per volume, as Applicants teach and currently claim. Moreover, Applicants assert that the teachings of Medenica relate to compositions and methods for treating cancer and immune diseases, not hepatitis. Applicants have previously asserted in a Declaration under 37 C.F.R. §1.132, and have provided evidence in support of such assertions, that the findings in the present application were certainly unexpected given the patient population under study and the fact that no other medications currently available for treating hepatitis patients have been shown to reverse the disease process, as

demonstrated by both liver function tests and liver histopathology, such as that shown in the present application.

Applicants submit that based on the foregoing amendment to the claims, **Medenica does not teach or suggest** the compositions of the instant invention.

Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

B. The Examiner has maintained the rejection of claims 1, 2, 5 and 7 under 35 U.S.C. §102(b) as being anticipated by Shawkat (U.S. 5,648,089) for the reasons cited in the previous Office Action. The Examiner alleges that Shawkat teaches using *Nigella sativa* in an oral herb composition to treat patients diagnosed with active Hepatitis B and Hepatitis C.

Applicants' Invention as Currently Claimed

As noted above, Applicants' invention, as currently claimed, is directed to a pharmaceutical composition, comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa* and *Ranunculus arvensis*, or extracts thereof, and a pharmaceutically acceptable carrier. More particularly, the claims have been amended to reflect that the composition contains at least one of the botanical plants in a concentration of not less than 20% weight per volume. In another embodiment, the present invention is drawn to a composition comprising a therapeutically effective amount of *Nigella sativa* and *Anemone hepatica*, or extracts thereof. This particular embodiment contains *Nigella sativa* in a concentration of not less than 20% weight per volume. The composition may be delivered as a tablet or capsule, or in the form of a liquid or suspension. It may be delivered intramuscularly, subcutaneously, intravenously, intranasally, topically, transdermally, or in the form of a suppository. It may be used to treat hepatitis and to increase the number of immune cells and platelets in patients.

Moreover, one new independent claim and two new dependent claims have been added for consideration that recite the language from previously presented claims 1 and 2. More particularly, these new claims recite that the compositions as currently claimed

may be used for treating advanced stage hepatitis patients, characterized as having fibrosis and cirrhosis of the liver as well as for increasing immune cells and platelets in patients.

The Shawkat Reference

Shawkat teaches an herbal combination for treating viral hepatitis. This combination contains a dried mixture of nine different plants, one of which is *Nigella sativa*. Each plant is present in given percentages on a dry weight basis. Within this mixture of plants, the concentration of the dried powder from the seeds of *Nigella sativa* is 10%. Shawkat does not prepare any extracts from the plants in the mixture.

Claim Amendments and Arguments in Support of Patentability over Shawkat et al.

Applicants respectfully traverse the Examiner's rejection and again assert that in order for a rejection under 35 U.S.C. §102(b) to be proper, the reference(s) must recite each and every element of the invention as claimed. Applicants assert that Shawkat does not teach the compositions of the present invention as currently claimed and that there are distinct differences between the teachings of Shawkat and the present application.

For example, applicants assert that Shawkat teaches an herbal combination containing a mixture of nine different plants, one of which is *Nigella sativa*. The mixture of botanicals is alleged to be useful for treating viral hepatitis, and the percentage of *Nigella sativa* within the mixture is 10%. Moreover, Shawkat teaches clearance of viral DNA. Applicants assert that most forms of hepatitis virus, including hepatitis C virus, are RNA viruses, and accordingly, Shawkat is not enabling for such teachings and constitutes no more than a generic disclosure.

More importantly, Applicants assert that Shawkat **neither teaches nor suggests a pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa* and *Ranunculus arvensis*, or extracts thereof, and a pharmaceutically acceptable carrier**, wherein the at least one of the botanical plants is present in a **concentration of not less than 20% weight per volume**. In addition, **Shawkat does not teach or suggest a composition comprising a therapeutically effective amount of *Anemone hepatica* and *Nigella sativa*, or extracts**

thereof, wherein the *Nigella sativa* is present in a concentration of not less than 20% weight per volume. Furthermore, Shawkat does not teach or suggest that the currently claimed plant compositions can be used for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis and for increasing the number of immune cells and platelets in patients having advanced stage hepatitis characterized by fibrosis and cirrhosis, wherein the patients are in stage 4-6 of the disease process.

Moreover, Applicants assert that the herbal combination of Shawkat contains a **dried plant mixture** and that the *Nigella sativa* allegedly is present within the mixture at a concentration of 10%. Applicants assert that this composition differs from the compositions of the present invention since **Applicants' compositions comprise a not less than 20% weight/volume extract of at least one of the plants noted in claim 1.** Applicants further assert that the concentration of the active moiety from *Nigella sativa* in the Shawkat reference is much lower than that of Applicants' composition since Shawkat makes no attempt at releasing the active component by way of extraction. Applicants are cognizant of the side effects that are potentially troublesome if one uses the dried plant mixture, including gastrointestinal problems.

Applicants submit that based on the foregoing amendment to the claims, Shawkat **does not teach or suggest** the compositions of the instant invention.

Withdrawal of the rejection under 35 U.S.C. §102(b) is respectfully requested.

Rejection under 35 U.S.C. §103 (a)

A. The Examiner has maintained the rejection of claims 1 and 3-10 under 35 U.S.C. § 103(a) as being unpatentable over Medenica (U.S. 5,653,981) for the reasons set forth in the previous Office Action.

The Examiner alleges that Medenica teaches using an extract of *Nigella sativa* for increasing immune system function. The Examiner further alleges that Medenica teaches that the extract of *Nigella sativa* may be administered intramuscularly, subcutaneously, intravenously, by tablet, by capsule, or suppositories. The Examiner admits that Medenica does not teach or suggest the ingredients in the dosage forms or the amounts claimed by Applicant. However, the Examiner alleges that the dosage form or amount of a specific ingredient in a composition is the result effective parameter that a person of

ordinary skill in the art would routinely optimize. The Examiner alleges that optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ.

The Examiner fails to set forth a proper *prima facie* case of obviousness

Applicants maintain that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further maintain that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed; 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in making the combination to reach the invention as claimed.

The Examiner notes that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The Examiner further alleges that with regards to the dosage form or amount of a specific ingredient, one skilled in the art would be motivated to modify the different dosage forms or amounts of a specific ingredient to see which form or amount would work best in the invention as taught by the reference.

Applicants respectfully traverse the Examiner's rejection and have amended the claims to better clarify what Applicants believe to be the invention. In particular, as noted above, Applicants have amended claim 1 to recite:

"A pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa* and *Ranunculus arvensis*, or extracts thereof, and a pharmaceutically acceptable carrier, wherein the at least one of the botanical plants is present in a concentration of not less than 20% weight per volume."

Moreover, also as noted above, claim 2 has also been amended to recite:

"A pharmaceutical composition comprising a therapeutically effective amount of *Anemone hepatica* and *Nigella sativa*, or extracts thereof, and a pharmaceutically

acceptable carrier, wherein the *Nigella sativa* is present in a concentration of not less than 20% weight per volume.”

Applicants submit that it is no more than obvious to try different dosage forms or ingredients, and obvious to try has never been the proper standard for assessing obviousness. Even if, *assuming arguendo*, one of ordinary skill in the art found such dosage forms or ingredients obvious to use, the present invention is still patentable for at least the following two reasons:

1. Medenica does not teach or suggest a pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa* and *Ranunculus arvensis*, or extracts thereof, and a pharmaceutically acceptable carrier at a concentration of not less than 20% weight per volume. Furthermore, there is no teaching that the composition as claimed in amended claim 1 may be used for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis wherein the patients are in stage 4-6 of the disease process. In addition, there is simply no teaching or suggestion that the composition as claimed can be used to increase the number of immune cells and platelets in patients.

2. Medenica does not teach or suggest a pharmaceutical composition comprising a therapeutically effective amount of *Anemone hepatica* and *Nigella sativa*, or extracts thereof, and a pharmaceutically acceptable carrier, wherein the *Nigella sativa* is present in a concentration of not less than 20% weight per volume. Furthermore, there is no teaching that the composition as claimed in amended claim 2 may be used for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis wherein the patients are in stage 4-6 of the disease process. In addition, there is simply no teaching or suggestion that the composition as claimed can be used to increase the number of immune cells and platelets in patients.

Based on the foregoing, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

B. The Examiner has maintained the rejection of claims 1 and 3-10 under 35 U.S.C. §103(a) as being unpatentable over Shawkat (U.S. 5,648,089). The Examiner alleges that

Shawkat teaches using *Nigella sativa* in an oral herb composition to treat patients diagnosed with active Hepatitis B and Hepatitis C. The Examiner admits that the reference does not specifically teach the ingredients in the dosage forms claimed by Applicants. However, the Examiner alleges that the dosage form or amount of a specific ingredient in a composition is the result effective parameter that a person of ordinary skill in the art would routinely optimize. The Examiner alleges that optimization of parameters is a routine practice that would be obvious for a person of ordinary skill in the art to employ.

The Examiner fails to set forth a proper *prima facie* case of obviousness

As noted above, Applicants assert that a rejection under 35 U.S.C. §103 is proper only when a prior art reference alone or in combination with a second prior art reference renders the invention obvious. Applicants further assert that a rejection based upon a combination of references is not proper unless the following three criteria are met: 1) the references in combination teach every single element of the invention as claimed; 2) there must be some suggestion or motivation in the prior art to combine the references to reach the invention as claimed; and 3) there must be a reasonable expectation of success in making the combination to reach the invention as claimed.

The Examiner notes that a recitation of the intended use of the claimed invention must result in a structural difference between the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. The Examiner further alleges that with regards to the dosage form or amount of a specific ingredient, one skilled in the art would be motivated to modify the different dosage forms or amounts of a specific ingredient to see which form or amount would work best in the invention as taught by the reference.

Applicants respectfully traverse the Examiner's rejection and as noted above, have amended the claims to better clarify what Applicants believe to be the invention. In particular, Applicants have amended claim 1 to recite:

“A pharmaceutical composition, comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa*, and *Ranunculus arvensis*, or

extracts thereof, and a pharmaceutically acceptable carrier, wherein the at least one of the botanical plants is present in a concentration of not less than 20% weight per volume.”

Moreover, claim 2 has also been amended to recite:

“A pharmaceutical composition comprising a therapeutically effective amount of *Anemone hepatica* and *Nigella sativa*, or extracts thereof, and a pharmaceutically acceptable carrier, wherein the *Nigella sativa* is present in a concentration of not less than 20% weight per volume.”

Applicants submit that it is no more than obvious to try different dosage forms or ingredients, and obvious to try has never been the proper standard for assessing obviousness. Even if, *assuming arguendo*, one of ordinary skill in the art found such dosage forms or ingredients obvious to use, the present invention is still patentable for at least the following three reasons:

1. Shawkat does not teach or suggest a pharmaceutical composition comprising a therapeutically effective amount of at least one of the botanical plants selected from the group consisting of *Actaea rubra*, *Anemone hepatica*, *Anemone nemorosa*, *Nigella sativa* and *Ranunculus arvensis*, or extracts thereof, and a pharmaceutically acceptable carrier, wherein the plant compositions must be administered at a concentration of not less than 20% weight per volume, as taught and currently claimed by Applicants. Furthermore, there is no teaching by Shawkat that the composition as claimed in amended claim 1 may be used for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis wherein the patients are in stage 4-6 of the disease process. In addition, there is simply no teaching or suggestion by Shawkat that the composition as claimed can be used to increase the number of immune cells and platelets in these patients.

As noted in the Declaration previously filed by Applicants on June 29, 2005, the findings of Applicants were unexpected in that the hepatitis patients under treatment were at such a late stage in the disease process that an actual improvement in clinical parameters and a reversal of the disease process has never been observed with any other current treatment strategy, including that taught by Shawkat. Applicants further attested to the fact that a composition comprising the plant extracts at less than a 20% weight per

volume concentration was not effective in this very sick subset of hepatitis patients showing signs of liver cirrhosis and necrosis.

2. Shawkat does not teach or suggest a pharmaceutical composition comprising a therapeutically effective amount of Anemone hepatica and Nigella sativa and a pharmaceutically acceptable carrier, wherein the Nigella sativa is present in a concentration of not less than 20% weight per volume. Furthermore, there is no teaching that the composition as claimed in amended claim 2 may be used for treating patients having advanced stage hepatitis characterized by fibrosis and cirrhosis wherein the patients are in stage 4-6 of the disease process. In addition, there is simply no teaching or suggestion that the composition as claimed can be used to increase the number of immune cells and platelets in patients.

Based on the foregoing, withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Neither Shawkat nor Medenica teaches or suggests a pharmaceutical composition comprising at least one plant selected from the group consisting of Actaea rubra, Anemone hepatica, Anemone nemorosa, Nigella sativa and Ranunculus arvensis, and a pharmaceutically acceptable carrier, wherein the at least one of the botanical plants is present in a concentration of not less than 20% weight per volume. In addition, neither Medenica nor Shawkat teaches or suggests a composition comprising a therapeutically effective amount of Nigella sativa and Anemone hepatica, or extracts thereof, and a pharmaceutically acceptable carrier, wherein the Nigella sativa is present in a concentration of not less than 20% weight per volume. Moreover, there is no suggestion or motivation for treating stage 4-6 (advanced stage) hepatitis patients having evidence of liver fibrosis and/or cirrhosis using the compositions of the present invention, since these unexpected findings were not known until the time of the present invention. Moreover, there is no suggestion or motivation to use the compositions of the present invention for increasing the number of immune cells and platelets in this patient population.

3. The present compositions provide unexpectedly superior therapeutic effects. In particular, no one to date, including Medenica and Shawkat, has taught or suggested, much less demonstrated, that the compositions as claimed could be useful clinically to improve liver function and liver histopathology, as well as to enhance the immune function in hepatitis patients at a late stage of the hepatitis disease process, particularly when fibrosis and cirrhosis are evident. Furthermore, the dose used for treating these late stage hepatitis patients differs significantly from the doses of Shawkat and Medenica, as was evident in the declaration under 37 C.F.R. §1.132 signed by Dr. Ismail Elchagea, as previously submitted. Accordingly, the dosages taught by Medenica and Shawkat would not prove effective, since in both cases, lower concentrations, in particular, 2.2% and 10%, were used, respectively. The higher doses of the composition as claimed by Applicants of the present invention were necessitated by the advanced stage of the disease for which treatment was desired and for use in this particular subset of patients having advanced stage hepatitis, for which no other treatment options are available. To Applicants' knowledge, this is the only such therapy that is capable of improving liver function and histopathology and of reversing the liver damage observed in this patient population. More particularly, due to the presence of active fibrosis and cirrhosis in these advanced stage hepatitis patients, the lower doses taught by Shawkat and Medenica would not be effective. In addition, neither Shawkat nor Medenica has demonstrated effects of the plant composition as presently claimed, on platelet counts in this patient population. As noted above, the improvement in liver function and histopathology, as well as on the other noted clinical parameters and immune function in this patient population, was not appreciated by Shawkat or Medenica, since the need for higher doses could not be predicted until the findings of the current invention.

Applicants assert that the Shawkat and Medenica references, when used alone or in combination, do not teach or suggest the compositions of the presently claimed invention. **Neither Shawkat nor Medenica teaches or suggests the presently claimed plant compositions at the concentrations taught by the Applicants of the present invention.** Applicants further assert that the findings of the present application were unexpected given the fact no other therapies or compositions are available to treat or reverse the pathology associated with this late stage of the disease process. Thus,

successful treatment of this subset of hepatitis patients, who exhibit cirrhosis and necrosis, with the presently claimed compositions was unexpected due to the inability of existing therapies to aid in the improvement or reversal of liver pathology in this patient population.

It is Applicants' belief that the Examiner has tried to reconstruct Applicants' invention using hindsight reconstruction, which is impermissible.

Based on the foregoing, withdrawal of the rejection is respectfully requested.

Fees

A check in the amount of \$520. is enclosed to cover the Request for Continued Examination and the fee for the new claims. No other fees are believed to be necessitated by the instant response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment, or to credit any overpayments.

Conclusion

Applicants believe that in view of the foregoing, the claims are in condition for allowance. Withdrawal of the rejections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 118, to effect a resolution.

Respectfully submitted,



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Attachment: Request for Continued Examination
Check to cover RCE and newly added claims